The effects of apathy and depression on cognitive and functional outcomes in Alzheimer's disease.

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Declaration

This thesis is an original work and has not been submitted in part or whole in fulfilment of any other degree. The work of other scholars that have been used in this dissertation had been duly quoted, cited and referenced.

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Abstract

Alzheimer's disease (AD) is the most common cause of dementia initially characterised by short-term memory deficits followed by a progressive cross domain cognitive and functional decline over time and loss of independence in carrying out activities of daily living (ADL). Apathy and depression are also the two most frequent neuropsychiatric sequalae associated with AD and have an impact on patients' ability to execute ADLs. Little is still known if apathy subdomains differently predict ADL performance in these patients. In this study, we aimed to quantitatively investigate if global apathy and depression predict ADL performance. We also wanted to establish if the apathy evaluation scale (AES) items resolve into three factors as proposed by Marin and if those factors differently predict performance of ADLs. We recruited a sample of 115 patients diagnosed with probable or possible AD. Basing on current literature, we hypothesised that apathy and depression predict ADL performance. We also hypothesised that AES items will load into three factors relating to cognitive, behavioural and affective apathy subdomains and that these subdomains will differentially predict ADL performance in our patient sample. Our results indicated that high apathy and depression symptoms were associated with problems to carryout ADLs. They also indicated that AES items resolved into a three factor solution in analogy with Marin's conceptualisation but they did not cluster in the manner that he proposed. Finally, when these factors are regressed simultaneously, (derived from factor analysis) only behavioural apathy significantly predicted ADLs.

Key words: Alzheimer's disease, Activities of daily living, Apathy, Depression

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Introduction

Dementias are a cluster of neurodegenerative illnesses primarily characterised by progressive gross domain deficits such as memory problems, language difficulties and other higher order functions like problem solving. These illnesses affect roughly 50 million people globally with an estimated increment of 10 million people annually (Alzheimer 's Disease International, 2020; World Health Organisation, 2019). A large proportion (nearly 60%) of dementia cases are found in low-middle income countries (WHO, 2019). It is estimated that the proportion of the world's population over 60 years will nearly double from 12% to 22%, by 2050, with the majority of this population in Low and Middle Income countries (LMICs). With an aging population, there is also higher risk of age-related chronic diseases of the brain including dementia. Although LMIC's will account for an estimated 71% of all people living with dementia by 2050 (De Jager, Msemburi, Pepper, & Combrinck, 2017; WHO, 2019), limited research has been carried out in these developing countries, including South Africa. Few studies that have been conducted in some of these regions such as Latin America and Sub Saharan Africa reported an 8.5% and 10% prevalence rates respectively (de Jagar et al., 2017; Mavrodaris, Powell, & Thorogood, 2013). In South Africa, few prevalence studies that have been published have utilized small study samples. For instance, a study conducted by Van der Poel and Heyns (2012) on 200 black urban South Africans in Bloemfontein showed a 6% prevalence rate of dementing illnesses. Another study using a small clinical sample of coloured patients above 60 years of age reported an 8.6% prevalence of dementia cases (see Ben-Arie, Swartz, Teggin, & Elk, 1983 for review). Recently, a large dementia prevalence study was conducted in a low income IsiXhosa-speaking community. This study reported a 12% prevalence rate for dementia in people aged 60 years and above (de Jager et al., 2017).

The authors however caution that these rates might not be representative of the entire South African population partly due to small sample size and a non-representative sample of South African population. Conversely, in resource rich settings such as Europe, there is new evidence showing a decline in the prevalence rates of dementias which is in part attributable to lifestyle modifications (Wu et al., 2016). Similar trends have also been observed in the United States. For example, it is reported that from year 2012 to 2017, dementia prevalence rates dropped by 2.8 % and this decline has been partly linked to high levels of education in the US population (see Langa et al., 2017).

Alzheimer's disease (AD) is the most common form of dementia typically occurring in late adulthood (over 65 years) and accounts for between 60 to 70 % of dementia cases in this population (Baillon et al., 2019; Meyer, Harirari, & Schellack, 2016; Sosso, Nakamura, & Nakamura, 2017). In South Africa Alzheimer's disease features among the top 50 causes of death and the country is ranked 31st in the world in terms of AD as the cause of death especially in the geriatric population (see Meyer et al., 2016 for review). Although, the profile of progression of AD is variable, the average life expectancy post diagnosis typically ranges between 3 and 9 years (Sosso et al., 2017). However, the evolution of AD symptoms does not follow the same trajectory. There are other clinical phenotypic variant presentations of Alzheimer 's disease that do not follow the typical pattern. These variants include non-amnestic focal cortical syndromes, such as primary progressive nonfluent aphasia, logopenic aphasia, posterior cortical atrophy, and frontal variant Alzheimer's disease. These are generally referred to as atypical Alzheimer's diseases (Eratne et al., 2018).

In typical Alzheimer's disease, observable symptoms starts around age 65 as late onset Alzheimer's disease (LOAD). However, between 4-5% of AD cases present before the traditional cut off age of 65 years as early onset Alzheimer's disease (EOAD) (Sosso et al., 2017). Although the underlying histopathological composition of AD is the same regardless

of age of onset (Baillon et al., 2019), there is evidence from some studies suggesting that there are differences in the pathophysiology and clinical manifestation of EOAD and LOAD. These studies suggest that EOAD is rapidly progressive resulting in rapid cognitive decline, increased behavioural deficits and is also non-amnestic in 33% of the cases while LOAD clinically presents with an insidious and progressive deterioration of episodic memory followed by a progressive cognitive decline over time resulting in attenuation of function in other domains such as language, praxis and executive functions (Baillon et al., 2019; Eratne et al., 2018; Ferreira et al., 2017; Han, Nguyen, Stricker, & Nation, 2017; Schindler et al., 2017). Pathophysiologically, EOAD is associated with posterior brain involvement, cortical atrophy, limited cerebral blood flow and low glucose metabolism, especially in parieto-temporal brain structures. This therefore explains why focal cortical fallouts such as aphasias, apraxias and agnosias precede memory problems in the clinical presentation of EOAD (Ferreira et al., 2017; Ossenkoppele et al., 2012).

Biomarkers of Alzheimer's disease

The neuropathologic changes that take place in the evolution of AD happens around a decade before progressing into a full dementia (Alzheimer's Disease, 2020; Price et al., 2009; Schindler et al., 2017) thus making early detection of AD difficult, when treatment would potentially be more effective. In addition, current treatment approaches have largely focused on alleviating AD symptoms temporarily but fail to relief the underlying degenerative process (Price et al., 2009; Schindler et al., 2017). In light of this, empirical attention has been directed at identifying reliable biomarkers for early detection of AD, with a potential for a promising therapeutic window opening. Much of research in this area have focused on genetics, blood and cerebrospinal fluid neurochemical components that can serve as predictors of AD.

Genetic Biomarkers: A number of genetic studies have been conducted investigating the genetic profile of AD patients in comparison to healthy people (e.g., Jack Jr & Holtzman, 2013; Jack et al., 2018; Lambert et al., 2009). These studies collectively seem to suggest that EOAD cases, especially, familial EOAD, mostly include autosomal dominant variant of AD, which results from genetic mutation in either of the 3 genes namely, amyloid-β precursor protein (AβPP), presenilin-1(PSEN1) and presenilin 2 (PSEN2) found in chromosomes 21, 14 and 1 respectively. Conversely, LOAD is associated with mutation in genes such as apolipoprotein (APOE), bridging intergrator 1 (BIN 1) region, clustering (CLU), phosphatidylinositol clathrin assembly lymphoid-myeloid (PICALM), and complement receptor 1 (Huynh & Mohan, 2017). Genetic studies have shown that of all the genetic biomarkers of LOAD, apolipoprotein seem to be the most promising biomarker of preclinical AD (Huynh & Mohan, 2017; Alzheimer, Disease International, 2020). In humans, one of the three variants of this gene (APOE) are inherited from each parent prenatally. These are ε2, ε3 or ε4. However, ε4 allele is the one mostly attributed to predisposing one to developing AD compared to other alleles. Furthermore, the presence of ε4 increases the likelihood of the accumulation of cerebral beta amyloid (ADI, 2020; Loy, Schofield, Turner, & Kwok, 2014; Michaelson, 2014) which is known to be one of the histopathological hallmarks of AD (Johanson et al., 2019).

CSF-Derived biomarkers: The histopathological signature of typical AD is marked by an initial accumulation of amyloid plaques (mainly amyloid β peptides). The main Aβ peptide that aggregates in the cortex and medial temporal lobe structures is Aβ42 causing significant synaptic damage in these areas. Extensive research has thus been focused on this Aβ peptide (e.g., De Jong, Jansen, Kremer, & Verbeek, 2006; Jack Jr et al., 2018; Kapaki, Paraskevas, Zalonis, & Zournas, 2003). The exact mechanism of how Aβ42 aggregates in these brain parts is unclear. However, two hypotheses have been proposed: 1) this could arise

due to overproduction of Aβ42, and/or 2) a suppressed Aβ42 venous drainage into the CSF. These two processes lead to a cumulative Aβ42 reduction in the CSF (Liu, Kanekiyo, Xu, & Bu, 2013). This reduction could therefore serve as one of the key diagnostic tools in preclinical AD. In fact, Kapaki and colleagues (2003) found that there was a 0.5 fold Aβ42 CSF decrease in AD patients compared to a control group. A Subsequent study by De Jong et al. (2006) also yielded similar results. In addition to amyloid plaques, neurofibrillary tangles (primarily tau and phosphorylated tau) also accumulates in the cerebral cortex and medial temporal lobe structures in the early phases of AD (Huynh & Mohan, 2017; Schindler et al., 2017). The accumulation of amyloid plaques and neurofibrillary tangles in temporal lobe structures such as the hippocampus, amygdala and the entorhinal cortex (which are involved in learning and recall of previously learnt content) explains why an amnesic presentation predominates the clinical manifestation of AD (Peña-Casanova, Sanchez-Benavides, De Sola, Manero-Borras, & Casals-Coll, 2012; Schindler et al., 2017). As the disease progresses, these intra cytoplasmic inclusions (amyloid plaques and neurofibrillary tangles) spread to other areas of the brain resulting in progressive impairment in other cognitive abilities, producing impairments such as word finding difficulties, visuospatial problems, and dysexecutive problems (Peña-Casanova et al., 2012). There is also attenuation in functioning, mobility, continence and increasing dependence on others for activities of daily living (ADL's). Consequently, patients with AD end up requiring around the clock care. As brain function gradually deteriorates, death can result because of major disorders of the central nervous system (Peña-Casanova et al., 2017; Eratne et al., 2018; Soso et al., 2017).

Blood-derived biomarkers: In recent years, research has shifted from investigating potential biomarkers of AD harnessed from invasive sources such as CSF to non-intrusive ones such as blood. Research in this arena has since accelerated and has yielded blood components such

as plasma proteins, lipids and MicroRNAs that can be useful potential biomarkers for detection of pre symptomatic AD (De Marshal et al., 2019; Huynh & Mohan, 2017).

Diagnosis of Alzheimer's disease

The clinical manifestation and characteristic symptomatology of mild cognitive impairment (MCI) and AD is usually recognisable in clinical assessment. However, given that changes in brain function and structure are the earliest signs of AD, followed by cognitive and functional impairment, AD diagnosis is made following comprehensive neurological, cognitive, functional, neuroimaging and biomarker assessments (Alzheimer's disease, 2020; Eratne et al., 2018). It is however noteworthy that a definitive diagnosis of AD can only be made during autopsy with corroborative histopathological evidence of intracytoplasmic inclusions in the brain. Nonetheless, in clinical settings, diagnostic terms such probable and possible AD are usually used. The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984) has developed symptom profiles of these two diagnostic categories. For a diagnosis of probable AD, there should be (1) evidence of dementia symptoms, which are not attributable to any neurological, psychiatric or systemic pathologies, 2) progressive amnesic syndrome, 3) presence of a comorbid neurological or systemic illness that can result in a dementing process but is not the underlying cause. Conversely, possible AD is characterised by 1) evidence of dementia derived from clinical interviews and neurocognitive assessments, 2) More than two observable cognitive deficits and progressive deterioration of memory 3) no altered consciousness.

Current treatment for Alzheimer's disease.

There is currently no approved pharmacological treatment of AD. Currently prescribed medical regimes do not stop the underlying neuro-degeneration of this disease but only alleviate the associated symptomatology. Given that the common underlying

neurochemical dysfunction associated with AD is cholinergic neuronal loss, the preferred pharmacologic treatment for AD has as such been the manipulation of acetylcholine synaptic activity. Four typically prescribed cholinergic agents in the treatment of AD are tecrine, donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl) and memantine (Ebixa). These agents inhibit the activity of the enzyme acetylcholinestrase postsynaptically thus increasing the synaptic activity of acetylcholine (Alzheime's disease international, 2020; DeMarshall, et al., 2019; Morrison & Lyketsos, 2005). Although tectrine is also a treatment option for AD, it is rarely used in other countries such as the USA because of its potential neurotoxic effects (Casandra et al., 2016). Because AD has no known cure, the above mentioned drugs are used to treat symptoms or to stop them progressing for a while.

There are other non-pharmacological interventions that are often used for AD patients. These treatment modalities are primarily employed to maintain and/or improve the cognitive capacity of the patient, ADLs performance and also to reduce the impact of neuropsychiatric fallouts (e.g., apathy, depression, agitation, & sleep problems) associated with AD. These treatment options include computerised memory training, cognitive behavioural therapy (CBT) and music therapy (Ishii et al., 2009; ADI, 2020). However, just like pharmacological prescriptions, these interventions do not stop the underlying neural loss characteristic to AD.

Alzheimer's disease and Activities of daily Living

AD results in gradual functional decline and loss of independence in carrying out activities of daily living (ADLs) (Etrane et al., 2018; Fujita, Notoya, Sunahara, Nakatani, & Kimura, 2018; Martyr & Clare, 2012). Generally, ADLs differ in complexity and level of difficulty. They typically cluster into two categories; 1) basic activities of daily living (BADLs) and 2) instrumental activities of daily living (IADLs). BADLs involve activities that a person carries out in his/her day to day self-care such as self-hygiene, dressing,

eating/feeding and toileting. They are more associated with motor dysfunction rather than cognitive fallouts and are often preserved in the early stages of AD (Martyr & Clare, 2012; Mioshi et al., 2007). In contrast, IADLS are a cluster of complex daily routines that underlie living independently. These activities include, for example, managing finances, shopping and medical adherence. Loss of autonomy in carrying out IADL's is often proportionate to the patient's cognitive status and these IADLs are more vulnerable to the cumulative effects of AD (Martyr & Clare, 2012; Mioshi et al., 2007). In the presentation of AD, IADL's are negatively affected first, and problems in BADLs follow because of the reduction in performing IADLs. Evidence also suggests that the cognitive dysfunction associated with memory loss is linked to IADLs impairments observed in early phases of AD (e.g., Fujita et al., 2018). In addition, Fujita et al. (2010) also found that constructional ability, working memory, executive function and episodic memory influenced IADLs. These empirical findings seem to suggest that a malfunction of various cognitive processes could lead to disturbances in conducting ADLs, particularly IADLs. Mioshi and colleagues (2013) found that dysfunctions in carrying out IADLs was linked to diffuse cortical (temporal, posterior cingulate, frontal, parietal) and sub-cortical (caudate) atrophy. The pattern of disruption of activities of daily living is further complicated by the presence of neuropsychiatric symptoms.

Neuropsychiatric outcomes of Alzheimer's disease

Although Alzheimer's disease is generally understood to be a neurocognitive disorder, almost all of the patients diagnosed with AD develop neuropsychiatric symptoms (NPS) during the course of their illness (Burke, Golfarb, Bollam, & Khokher, 2019; Lyketsos et al., 2011). These neuropsychiatric symptoms otherwise known as behavioural and psychological symptoms of dementia (BPSD) are defined as psychological symptoms marked by "distortions of perception, thought content, behaviour, or affect" (Tamela et al., 2015, p.94).

The NPS spectrum include anxiety, irritability, aggression, delusions, apathy, depression, psychosis, and sleep problems (Johanson et al., 2019; Kiely, Mortby, & Anstey, 2017; Lyketsos et al., 2011). There is ample evidence in the literature showing that the comorbidity of NPS and AD is associated with accelerated progression of AD, poor prognosis, heightened levels of disability and care giver distress (Burke et al, 2019; Ferreira et al., 2017; Tamela et al., 2015).They have also been shown to increase the likelihood of mild cognitive impairment converting to a full AD picture (Ferreira et al., 2017; Ginsberg et al., 2019). Although the impact of NPS in the evolution of AD is widely recognised, they are often neglected in research and intervention protocols compared to cognitive and functional fallouts associated with AD. Of all the neuropsychiatric outcomes that are usually comorbid with AD, depression and apathy are the most prominent and are reported to be reliable predictors of disability and early institutionalisation (Benoit et al., 2012; Burke et al., 2019).

Neurobiology of NPS in Alzheimer's disease

Empirical work on the pathophysiology of AD has largely focussed on the cortex (e.g., Casanova et al., 2012; Ferreira et al., 2017; Ossenkoppele et al., 2012; Schindler et al., 2017). However, different neuropsychiatric syndromes observed in the progression of AD pathology are underpinned by different neural substrates including subcortical forebrain, diencephalic and brain stem nuclei that are linked with emotions and goal directed behaviour (Lancot et al., 2017). The pathologic changes that takes place in the evolution of AD also take place in some components of the limbic circuitry (such as the amygdala), basal forebrain bundles, substantia nigra, hypothalamus and the brain stem (Lancot et al., 2017; Schneider et al., 2006). These structures are also implicated in neuropsychiatric symptomatology. For instance, the amygdala and hypothalamus have been implicated in emotional regulation (Tamela et al., 2015). Understanding the clinical picture of AD in light of the neuropathology

of NPS could improve therapeutic approaches targeting these NPS in AD given that current pharmacologic treatment for some of these syndromes temporarily abate the symptoms and fail to target the underlying neural concomitants (Lancot et al., 2017).

Depression in Alzheimer's disease

Empirical work on AD and depression have shown that almost half of patients with AD suffer from depression at some point during the course of illness (Burke et al., 2019; Di Iulio et al., 2010). However a systematic review conducted by Chi and colleagues (2015) indicate that the prevalence of depression on AD patients vary by diagnostic approaches. For instance, using the DSM 5 criteria, prevalence rates are around 12.7% while they are about 40% in studies using criteria specific measures specific to AD such as the National Institute of Mental Health- depression in AD (Chi et al., 2015; Olin et al., 2002). Cognitive impairment (also characteristic in AD) is a risk factor for late life depression and there is a bidirectional relationship between the two conditions. There may be psychological drivers for depression risk in cognitively impaired individuals (Fujita et al., 2018) but in relation to biological risk factors, studies have identified neuropathological correlates that are common to both conditions. For example, cortical neural changes in brain areas such as the hippocampus, fronto-striatal and frontal limbic circuitry and deep white matter lesions are common in both of these illnesses (Burke et al., 2019). Additionally, amyloid plaque deposition which is also common in the pathophysiology of AD is also associated with depression (Johanson et al., 2019). In fact, Burke and colleagues (2019) suggest that patients with a comorbidity of AD and depression appear to have more neuropathology especially the accumulation of intracytoplasmic inclusions such as amyloid plaques and tau.

Although mild cognitive impairment is generally considered a prodromal phase of dementias including AD, the presence of geriatric depression in AD has also been shown to accelerate this conversion of MCI to a full dementia (Donovan et al., 2015; Ginsberg et al.,

2019). Depressive symptoms in AD decrease quality of life and often results in rapid functional decline and greater impairment in activities of daily living. Consequently, depression in AD has been associated with significant volitional decline (Fujita et al., 2018), which probably explains why it in turn affect IADLs performance in these patients. However, the diagnosis of depression in AD patients especially in late adulthood is often difficult largely because these patients in most cases do not meet the diagnostic criteria for depressive disorders. They instead typically present with symptoms dimensions such as lack of sleep, anorexia and fatigue that are not specific indices of depression (Burke et al., 2009). Consequently, the diagnosis of depression has largely been missed in the elderly which has potentially hindered treatment in these patients increasing morbidity and mortality (Burke et al., 2009).

Diagnosis of Depression in Alzheimer's disease

The diagnosis of depression is primarily conducted through a structured clinical interview and psychometric assessment. However, the diagnosis of geriatric depression is often challenging, especially in the context of AD primarily because seniors tend to present with less specific symptomatology (e.g., insomnia, fatigue, & appetite variations) which are not adequate for a diagnosis of depression as per the DSM 5 criteria for instance (APA, 2013; Burke et al., 2019). In addition, the elderly generally seem to under report depressive symptoms and instead attribute their states to normal response to life challenges and and/or part of aging process (Burke et al., 2019). For a diagnosis of depression using the DSM 5 criteria, the patient should present with more than four symptoms that characterise depression and these symptoms should not be attributable to substance abuse or comorbid illnesses (See APA, 2013 for a detailed review). The National Institute of Mental Health also developed a diagnostic criteria specific for depression in AD (Onlin et al., 2001) which was adapted from the DSM IV diagnostic criteria for major depressive disorder (APA, 2000). According to this

provisional diagnostic criteria, the patient should present with at least three of depressive symptoms and cognitive deficits such as attenuated capacity to think and concentrate were removed (Burke et al., 2019; Onlin et al., 2001).

Assessment of Depression in Alzheimer's disease

There are various geropsychiatric assessment measures (rating scales and structured interviews) available to quantify and characterise depression in dementias. However, most of these measures especially rating scales (e.g., Beck's depression Inventory; Beck, Steer., & Brown, 1996) except the Cornell Scale for Depression in Dementia (CSDD) were not developed and validated for older patients and also contains somatic symptoms. Given that there is substantial overlap between geriatric depression and other physical pathologies, these assessment instruments may inflate depression in the elderly and pose potential challenges in treatment of this neuropsychatric condition (Balsamo, Cataldi, Carlucci, Padulo, & Fairfield, 2018). The CSDD (Alexopoulos, 1988) has been adapted for depression in AD and has been shown to detect improvement in depressive symptoms in dementing patients post treatment (Baquero & Martin, 2015; Burke et al., 2019). The CSDD is a 19 item instrument that is widely used to measure depression in dementing diseases possibly because it includes information from the caregivers and also allows for differentiating cognitive and mood symptoms (Baquero & Martin, 2015). The neuropsychiatric inventory (Cummings et al., 1994) is another widely used assessment measure of depression in different neurological diseases.

Apathy in Alzheimer's disease

Although depression has received considerable scholarly attention in AD research, there has been an emerging strand of research recently suggesting that apathy is the most persistent and frequent neuropsychiatric sequalae observed in AD patients throughout all the levels of disease progression and also reliable predictor of MCI to AD (Hernandez et al.,

2012; Nobis & Husain, 2018; Umucu et al., 2019).

Marin (1990) is credited for conceptually defining apathy as a distinct amotivational disorder of goal directed activity characterised by observable deficits in goal directed cognition, affect and behaviour that reflect motivational impairment. He proposed that apathy is often characterised by lack of self-initiation and/or effort, attenuated or irresponsiveness to both negative and positive events, at times with flat or unchanging affect and lack of insight and concern about one's impaired functioning. Marin (1991) suggested that these impairments should not be accounted for by altered consciousness and/or deficits in intellectual functioning.

Subsequent scholars also followed Marin' conceptualisation of apathy. For instance, Starkstein (2000) also conceptualized apathy as a disorder of motivation which can occur independently of other diseases associated with neural loss. He added duration (minimum of four weeks) to highlight the persistence of the disease. Similarly, van Reekum et al. (2005) also subdivided apathy into cognitive, behavioural and emotional subdomains.

Marin's conceptualisation of apathy and its symptoms remains largely dominant. However, there is still confusion regarding the proper definition of apathy and its nosological position against other disorders of goal directed activity. Subsequent to Marin's work (Marin, 1990; Marin, 1991), several empirical studies have been carried out in an attempt to reach a consensus on the definition of apathy and its symptom profile (e.g., Levy & Dubois, 2006; Robert et al., 2009; van Reekum, 2005). Some scholars question Marin's conceptualisation of apathy as a disorder of motivation. For instance, Levy and Dubois (2006) suggest that lack of motivation cannot be directly assessed and does not readily point to the underlying pathological anatomy of apathy. They alternatively conceptualise apathy as a clinical syndrome characterised by a quantifiable reduction in self-initiated voluntary and purposeful activities that has a clear neuropathological base. According to this contemporary view,

apathy results from insults in the basal ganglia-prefronto cortical pathway, which is generally understood to be involved in the generation and control of goal directed behaviour (Levy & Dubois, 2006).

In light of the controversy surrounding the definition, nosological position, and diagnostic criteria for apathy. Robert et al. (2009) recently proposed a standard diagnostic guideline for the diagnosis of apathy in AD patients. The diagnostic criteria suggested by these authors require apathy symptoms to persist for a period of at least four weeks with impairments in at least two of the three symptom subdomains that constitute apathy (ie., goal directed behaviour, cognition and affect). Consequently, the symptoms should cause significant impairment to the general functioning of the patient, and should not be attributable to other causes such as physical disability, substance abuse, or other disorders that can mimic apathy symptoms (Robert et al., 2009). This diagnostic criteria have been shown to be a reliable predictor of apathy in clinical samples (see, (Mulin et al., 2011 for a detailed review).

It is estimated that up over 50%of AD patients develop apathy in the early phase of AD and this neuropsychiatric symptomatology worsens with the progression of the primary disease process (Hernanderz et al., 2012; Wouts, van Kessel, Beekman, Marinissen, & Voshaar, 2019). In general, apathy is associated with deleterious outcomes on cognitive functioning, interpersonal relationships, occupational activities, general health (Ishii et al., 2009; Landes, Sperry, & Strauss, 2005; Raimo, Trojano, Gaita, Spitaleri, & Santangelo, 2019) and its symptoms are also related to an attenuation in the capacity to carryout ADLs in AD patients (Ishii et al., 2009; Wouts et al., 2019; Raimo et al., 2019). These behavioural deficits (usually evidenced by lack of concern for ones hygiene, poor dietary choices and decreased motivational drive) often result in a poor prognosis, poor treatment compliance and quality of life, thereby increasing the chances of caregiver distress and early institutionalisation (Hernanderz et al., 2012; Njomboro & Debb, 2014; Raimo et al., 2019). In

It is however noteworthy in the earlier phase of AD, patients with apathy symptoms generally have the capacity to perform some basic routines such as eating, bathing and using the toilet but ability to carry out complex activities requiring executive input such as shopping, and budgeting is compromised (Futjita et al., 2017; Lechowski et al., 2009). This is not surprising because intact executive abilities are suspected to be necessary to effectively initiate, plan and motivate goal directed behaviour (Ginsberg, 2020). Given that apathy is also associated with lower adherence to treatment, it has the potential to complicate therapeutic process in co morbidities while also increasing the burden of comorbidities (Butterfiled et al., 2010; Chase, 2011).

While much is known about the role of apathy symptoms in the manifestation of AD and ADL performance, research specifically investigating the relationship between subdomains of apathy and ADLs is still at its infancy. An understanding of this association might be crucial in treating apathy because these subdomains may be differently associated with the patients' level of functioning. However, given that some subdomains of apathy and ADL dysfunction has common neuropathology, it can be inferred that they might be associated. For instance, cognitive apathy and a decline in the capacity to carryout out complex ADLs is associated with frontal atrophy. Similarly, behavioural apathy and IADL attenuation was associated with fronto parietal involvement (Mioshi et al, 2013).

Assessment of Apathy in AD

A number of scales are currently available to quantify the severity of apathy in dementing illnesses. In clinical practice, both multi item and single item scales are used to quantify and characterise apathy. Of these measures, the most widely used scale in the assessment of apathy in AD is the 18-item apathy evaluation scale (AES; Marin, 1990) which was developed alongside the original neuropsychiatric definition of apathy. Three versions of this scale exist, a clinician rated, informant rated, and self-rated version. The apathy

evaluation scale is mostly used because it has good psychometric properties. For instance, Marin (1991) found the scale to be valid and reliable when it was validated on various clinical cohorts including Alzheimer' disease, stroke and major depression. Such superior psychometric properties were also maintained using healthy adults (see Marin, 1991). Subsequent empirical work (e.g., Clarke et al., 2011; Starkstein, Petracca, Chemerinski, & Kremer, 2001) also yielded similar results. Recently the apathy evaluation (AES-S) has been shown to be a reliable measure of apathy in healthy middle aged participants who are at risk of developing AD (Umuncu et al., 2019).

The Neuropsychiatric inventory is another widely used assessment measure of apathy in dementia (Cummings et al., 1994). This instrument contains only one apathy item which measures its frequency and severity. Other apathy evaluation measures include the Lille apathy rating scale (Sockeel, Dujardin, Devos, Deneve, Destee, & Defebvre, 2006) and the frontal systems behaviour scale (Malloy & Grace, 2005).

Treatment of Apathy in AD

Although there has been growing research interest on apathy since the early 90s, the disorder is still under-assessed and under-diagnosed in clinical practice. As a result, there is no standard intervention protocols for apathy. Evidence showing the efficacy of currently used medication for apathy is still lacking. Evidence from clinical studies show that apathy in AD is associated with the dysfunction of the cholinergic and dopaminergic diffuse projecting pathways (e.g., David et al., 2008; Haegelen et al., 2009; Kobayashi, Ohnishi, Nakagawa, & Yoshizawa, 2016; Nobis & Husai, 2018; Rosenburg et al., 2013) and potential treatment trials have thus targeted these systems. Cholinesterase inhibitors such as donepezil and cholinergic precursor choline alphoscerate have been shown to improve overall cognitive function in AD (Kobayashi et al., 2016) and some studies have reported slight effects of this agent in abating neuropsychiatric symptoms in AD patients (e.g., Kobayashi et al., 2016; Wang et al., 2015).

However, cholinesterase inhibitors have not yet been empirically proven to be effective in long term treatment of apathy in AD patients (Nobis & Husain, 2018; Rea et al., 2014). Similarly, dopaminergic drugs such as methylphenidate, amantadine and bromocriptine have been shown to reduce apathy symptoms in AD (Campbell & Duff, 1997; Rosenburg et al., 2013; van Reekum et al., 2005). However, these agents have not been tested in randomised controlled trials. Over and above medical interventions, some psychotherapeutic interventions have been trialled in the treatment of apathy. These treatment modalities include cognitive behavioural therapy and music therapy (Ishii et al., 2009), although their efficacy is yet to be empirically established.

Apathy and depression.

Apathy and depression are often overlapping dimensions of behaviour in the presentation of AD. However, these two neuropsychiatric syndromes can occur independently (Landes et al., 2001, Benoit et al., 2012), suggesting that apathy and depression are separate entities. The substantial overlap of key symptoms of depression and apathy in AD has however made dissociating these two conditions difficult in some contexts (Landes et al., 2005; Zhu, Grossman, & Sano, 2019). The shared symptom dimensions between apathy and depression include anhedonia, loss of interest, and reduced level of activity (Levy et al., 1998; Starkstein Ingram, Garau, & Mizrahi, 2005). The difficulty in differentiating apathy from depression is also compounded by the fact that most traditional instruments that quantify depression have specific items that measure apathy (e.g., the Hamilton depression rating scale; Hamilton, 1976). Confusing apathy with depression can however have detrimental consequences in clinical practice. For example, patients with apathy can be misdiagnosed with depression and end up enrolled in depression medication regimens that have been shown to worsen their symptoms (Fava, Graves, Benazzi, 2006;

Hoehn-Saric, Lipsey, & Mc Leod, 1990; Wongpakaran, N., van Reekum, Wongpakaran T., & Clarke, 2007).

There is also converging evidence from multiple studies suggesting that apathy and depression are clinically and anatomically distinct (e.g., Levy et al., 1998; Njomboro & Deb, 2012; Starkstein et al., 2005). This body of work suggests that the presence of negative mood is very helpful in differentiating these two conditions (Landes, Sperry, & Straus, 2005). Negative affects like sadness, feelings of worthlessness and hopelessness, self-criticism and suicidal ideations which are typical of depressive syndromes do not form part of the clinical manifestation of apathy (Levy et al., 1998). Although the principal symptom for both apathy and depression is loss of interest; in patients with apathy, this reflects loss of motivation or ability rather than affective changes (Njomboro & Debb, 2014; Landes et al., 2005).

Apathy and depression also respond differently to psychopharmacological treatments, suggesting that these two conditions are neurochemically distinct. For example, apathy is usually treated with dopaminergic agonists such as amantadine and bromocriptine, because there is evidence of dopaminergic involvement in the suspected biological basis of apathy especially in Parkinson's Disease (PD) clinical samples (Zhou et al., 2020). These agents are however not useful in treating depression (Nobis & Husai, 2018; Rosenburg et al., 2013; van Reekum et al., 2005). The preferred treatment option for depression is the prescription of selective serotonin reuptake inhibitors and, sometimes antipsychotics (Burke et al., 2019; Chase, 2011). It is however noteworthy that research on the possible pharmacological treatment agents of apathy has largely been on very small samples and have not been tested in randomised controlled trials but are nonetheless promising (Chase, 2011; van Reekum et al., 2005). In addition, apathy is commonly comorbid in other progressive degenerative pathologies that nigrostriatal degeneration is largely absent including PD and AD (Zhou et al., 2020). The amyloidopathy associated with AD also seem to be a candidate determinant of

apathy compared to other psychiatric conditions including depression. For example, positron emission tomography (PET) studies have shown that patients with a double pathology of AD and apathy have heightened amyloidopathy compared to other clinical cohorts (e.g., Mori et al., 2014). Furthermore, studies using radiological data show that depression and apathy have different pathological anatomy. For example, apathy involves dysfunction in regions that constitute the anterior cingulate frontal-subcortical circuitry. These include anterior cingulate cortex, nucleus basalis, hippocampus, and medial forebrain regions (Chase 2011; Landes, Strauss, & Geldmacher, 2001; Levy & Dubois, 2006; Zhou et al., 2020). Conversely, depression is associated with neuropathology in frontal-striatal and subcortical limbic circuits, particularly, locus ceruleus, substantia nigra, hippocampus, and hypothalamus (Landes et al., 2001; see also Njomboro & Deb, 2012). Landes and colleagues (2001) propose that if some similar circuits are involved in the manifestation of apathy and depression, they differ in the degree of neurotransmitter involvement. For example, it widely appreciated that dopamine is known to be involved in feelings of pleasure and motivation and any dysfuction in the dopaminergic system partly explain the presence of apathy symptoms in the presentation of AD (Landes et al., 2001; Njomboro & Deb, 2012; Zhou et al., 2020).

Rationale and aims for the study

The impact of Alzheimer's disease on activities of daily living is well documented across several studies (e.g., Etrane et al., 2018; Fujita et al., 2018; Martyr & Clare, 2012; Mioshi et al., 2007). These studies also show that decline in carrying out ADLs contributes to poor health outcomes such as worsening of the symptoms, accelerated progression of AD and institutionalisation. It is therefore important to understand the predictors of ADL performance in AD in order to aid the development of intervention protocols. A number of cognitive and neuropsychiatric predictors of ADL performance have been identified. Whereas studies have consistently cited depression and apathy as the most common neuropsychiatric outcomes in

AD, their individual or comorbid effects on ADL performance in AD patients is poorly understood. (Benoit et al., 2012; Fujita et al., 2018; Chi et al., 2015). Although the effects of depression has attracted some scholarly work in this area, there is also emerging evidence implicating apathy symptoms in loss of autonomy in carrying out ADLs in AD patients (Hernanderz et al., 2012; Starkstein et al., 2006). However, little is still known about whether apathy subdomains differently associate with ADLs. There is also no quantitative evidence showing that apathy items (AES) resolve into a three factor solution in the manner proposed by Marin (1991). In this study we aimed to: 1) investigate the predictive effect of depressive and apathy symptoms after controlling for confounding variables such as age, gender and level of education, 2) To establish if AES items load into three factors (cognitive, behavioural and affective) as Marin (1991) suggested, and 3) to examine if each subdomain of apathy that we derived from factor analysis of AES items predict ADL performance differently. Based on previous academic literature, I hypothesised that higher levels of apathy and depression will be associated with less capacity to carryout ADL. I also hypothesised that apathy items (AES) will load into three factors (cognitive, behavioural and affective) and these subdomains will differently predict ADL performance in our sample. It has been reported elsewhere that apathy subdomains as conceptualised by Marin (1991) are associated with ADLs (Martyr & Clare, 2012; Mioshi et al., 2007).

Methods

Design and setting

This cross sectional study follows up on archival data collected in an ongoing process at the memory clinic at the Albertina and Walter Sisulu Institute of Ageing in Africa (IAA) in the department of Psychiatry and mental health at Groote Schuur hospital, Cape Town. The

data of all patients seen at the clinic is captured and stored. This data includes demographic information and psychometric assessment data. This study utilised such data. The data used in the study was collected in the period between year 2012 and year 2018. The data was from records of patients diagnosed with probable or possible AD. The principal clientele of the memory clinic are referrals from other health care facilities with mostly a query of a dementia. Generally, patients who visit the memory clinic are required to bring along their significant others who can provide collateral information. The entire process of seeing patients at IAA memory clinic is four staged.

In the first phase, a medical/psychiatric registrar conducts an intake interview, collecting the patient's medical history, demographic and biographical information in the process. In addition, an enquiry about the patients' current complaints and premorbid functioning is also made. In the second and third stages, which run concurrently, the patient undergoes physical and neuropsychiatric examination while his/her companion completes a battery of assessment measures such as the Apathy Evaluation Scale (AES), the Cornell Scale for Depression in Dementia **(**CSDD), and the Bristol Activities of Daily Living Scale (BADLS) in a separate location. During the third stage, a neurocognitive assessment is conducted with the patient. Some of the neurocognitive assessment measures that are administered during this stage test for orientation (Mini Mental Status Exam,) attention (Digit span) executive functions (cognitive switching). See table 1 and 2 for a detailed battery of tests and scales used at the clinic. In the final stage, a team of interdisciplinary health professionals from neurology, neuropsychology, psychiatry, geriatrics and other specialties meet in a case conference to explore different differentials and analyze brain scans to ultimately reach a diagnostic consensus. The team also discusses the patient's prognosis and intervention. Finally, the resident attending clinician then arranges a feedback session for the patient and his/her significant other where he/she informs them about the outcome of the assessments. All

patients' data collected during these assessments is stored in the patients file at IAA and an electronic copy is also created and stored in a database.

Table 1: Psychometric Measures used at Memory clinic

Subtest	**Domain**					
	Orientation	**Attention & WM**	**Memory**	**Executive functions**	**Perseveration**	**P. Speed**
1	MMSE	Digits (Forwards & backwards)	RBANS List test	Clock drawing	Luria's loops	Trail making
2			RBANS story telling test	Inhibition& Cognitive switching	Luria's hand sequences	
3			RBANS figure drawing			

NB: W.M = Working Memory
P. S = Processing Speed

Table 2: Scales used in Memory clinic

Neuropsychiatric domain	**Scale**
Apathy	Apathy evaluation scale(AES-I)
Depression	Cornell scale for depression (CSDD)
Activities of daily living	Bristol Activities of Daily Living scale (Modified)
Apathy & other psychiatric symptoms	Neuropsychiatric Inventory (NPI-D)

Participants

I collected archival participant data using non-probability purposive sampling from the patient medical folders from the IAA Memory Clinic. 500 medical folders were pulled for

investigation to see if they fitted the study purpose. However only 115 of those files were fitted the purpose of this study. These were files of patients who were diagnosed with AD. Data from Patients with other forms of dementias were excluded because this study was primarily targeting AD patients. In addition, patients with missing data were also excluded even if they had the requisite diagnosis (probable or possible AD) to be eligible for participation in this study. The missing data that particularly excluded participants included incomplete scales (apathy evaluation scale, Bristol activities of daily living scale and Cornell scale for depression) and other demographic data that was necessary for the analyses of this study. We also eliminated the data of patients with comorbid psychiatric diagnosis of major depressive disorders and bipolar to avoid their potential confounding influence. The age of the participants ranged from 42 years to 92 years (mean= 71 years, SD= 8.99). The sample comprised thirty eight (33%) males and seventy seven (67%) females. Majority (52%) of the participants were married. Forty three participants (37.4 %) had primary school and the same number also had secondary education (See table 1 below).

Table 3: Demographic characteristics of the participants

Variable		N	%
Sex			
	Male	38	33
	Female)	77	67
Marital status			
	Married	52	45.2
	Widowed	39	33.9
	Divorced	12	10.4
	Never married	12	10.4
HLOE			
	No Formal schooling	5	4.3
	Primary school	43	37.4
	Secondary School	43	37.4
	Matric	10	8.7
	College	9	7.8
	University	5	4.3

Measures

Apathy Evaluation Scale (AES). This is the widely used assessment measure of apathy that has been used across different patient samples including AD. It is a well-validated and reliable measure of apathy (Marin 1991). Three versions of this scale exist; a clinician rated, informant rated, and self-rated version. All the three versions of the AES are included in the memory clinic test battery. However, this study only used data derived from the AES-I because previous psychometric studies has shown that this version is the most robust detector of apathy relative to other versions (Clarke et al., 2011; Marin & Wilkosz, 2005). The AES-I (see Appendix A) comprise 18 items which has items such as: "S/he is interested in things", "S/he approaches life with intensity", "S/he puts little effort into anything" (Marin, Biedrzycki, et al., 1991). These AES-I items are measured on a four-point Likert-type scale (1 = not at all characteristic and 4 = a lot more characteristic). Possible attainable scores ranges from 18 to 72 with a lower score indicating less apathy. A total score above 37 suggest the possibility of apathy. Studies investigating psychometric properties of the AES-I suggest that this scale is reliable (Cronbach's alpha ranging from .86 to .94). It has also been found to be a valid assessment measure of apathy relative to other versions, $r = .50$, $p = .001$ (see, Clarke et al., 2011 for a detailed review).

Cornell Scale for Depression in Dementia (CSDD). The CSDD (Alexopoulos, 1988) is an assessment measure used to quantify and characterise depression in patients with dementing illnesses (Korner et al., 2006; Leontjevas, Gerritsen, Vernooij-Dassen, Smalbrugge, & Koopmans, 2012). This self-report measure contains 19 items each rated on a 4-point Likert-type scale. The scores ranges from 0-38. A score in the range of 10-17 indicates probable major depression while score above this threshold indicates definite depressive syndrome. Psychometric research on the CSDD suggest that this assessment tool has good validity and inter-rater reliability (Korner, et al., 2006; De Bellis & Williams, 2008). Its reported internal

consistency coefficient is .84, with a Cronbach's alpha of .6. The predictive validity is reportedly .75 (Amuk, Karadag, Oguzhanoglu, & Oguzhanoglu, 2003). CSDD also has a moderate to excellent detection of geriatric depression compared to other scales that measure depression (Korner et al., 2006; Leontjevas et al., 2012).

The Bristol Activities of Daily Living Scale (BADLS). The BADLS (see Appendix A) is a non-cognitive based instrument that is widely used to characterize ADL's in AD patients. (Byrne, Wilson, Bucks, & Wilcock, 2000). This assessment measure has 20 items and it is completed by the patient's caretaker or significant other. However, the IAA clinic utilizes the modified version of this scale, as such this study used the data derived from the modified version of the BDLS. The modified version contains 17 items measured on a five point Likert scale. The lowest attainable score is 0 while the maximum score is 51. Higher scores indicate that the patient is reliable on other people to carry out his/her ADLS (Bucks & Haworth, 2002). Empirical work on psychometric characteristics of BADLS suggest that this assessment measure is valid and reliable (See Bucks & Haworth, 2002). Psychometric studies of the BDLS are yet to be carried out in South Africa, but the scale is nonetheless commonly used in various health care facilities and research settings to screen for possible dementing illnesses. This is possibly because research conducted elsewhere has shown that the BDLS has superior psychometric properties (Bucks & Haworth, 2002).

Procedure

The procedure of collecting data at the Albertina and Walter Sisulu Institute of Ageing in Africa (IAA) is detailed above. However, for this study I did not use the electronic data at the clinic because the way such data was captured was not compatible with my analysis. Instead, I derived the data from hard copy patient files so that I can have the individual scores for all the scales that measured my variables. In addition, I corroborated the patients diagnosis from the folder with the electronic data. In cases of missing data, I looked for original patient's file from medical records to reconcile the missing data with what we have in the memory clinic data.

Statistical analysis

First, we ran bivariate correlations to establish if there was an association between our variables (demographics, depression, apathy and ADLs). We did the correlations using the total scores for our study variables. Second, we performed hierarchical multiple regression analysis to establish whether apathy and depression independently predict difficulties with carrying out ADLs after we partial out confounding variables such as age, gender, level of education and marital status. We controlled for these variables because they are known to exacerbate cognitive fallouts in dementias. For example, formal education seem to build the cognitive reserve and aid well-versed life decisions hence decelerating the cognitive deterioration associated with dementing illnesses (de Jager et al., 2017). Age is also the biggest risk factor for dementias (de Jager et al., 2017). Marital status in the elderly is also thought to play a role in the cognitive status in the context of AD. Being married seem to be associated with low cognitive fallouts (ADI, 2020) possibly because having a partner can provides one with social and cognitive engagement We first blocked the potentially confounding variables together in a regression equation and entered depression and apathy second in the equation, testing for the value and significance of incremental sums of squares across steps. Third, we performed an exploratory factor analysis to establish how AES individual items cluster together and also to see if they resolved into a 3 factor solution as proposed by Marin (1991). We then regressed the factors we derived from factor analysis on ADLS in a simultaneous regression equation. The regression models were checked to see that they met the standard regression assumptions e.g. homoscedasticity, normality of residuals etc. All the analysis was carried on statistical package for social sciences (SPSS) version 25. I set the significance level at 0.05 level.

Results

Our first aim was to investigate the relationship between our predictors (apathy and depression) and the ability to perform activities of daily living in our participants. To establish this relationship we performed a correlation analysis. Our results showed that apathy significantly correlated with the ability to carry out ADLs (0.288, p= 0.02). Similarly, depression also significantly associated with ADL performance (0.188, p= 0.045). Apathy and depression were also significantly associated (0.423, p= 0.00). These results are detailed in table 4 below.

Table 4 Correlations between study variables

	1	2	3	4	5
1.Age					
2. Sex	.006 NS				
3. ADls	.173 NS	-.136NS			
4.Depression	-**.185***	.110NS	**.188***		
5.Apathy	-.104 NS	.023NS	**.288****	**.423****	

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).
NS=Not significant: Significant statistics are in bold.

Hierarchical regression analysis

To investigate whether apathy and depression significantly predict ADL performance, we performed a hierarchical regression analysis. We also included age, sex and level of education and marital status as potential confounding variables. We hypothesised that deficits with the capacity to carryout ADLs will be related to apathy and depression and not explained by potential confounding variables. Our analysis indicate that apathy accounts for only 8.3% of the variation in ADL performance in our sample. However, when we include

depression, this value increases to 8.8%. Therefore depression accounts for only 0.5 % of the variance in ADL performance. The inclusion of potential confounding variables (age, sex, marital status & level of education) also increases the value to 20% implying that these variables account for an additional 11.2% of the total variance. For model 1 the F change was statistically significant (F(115, 1)= 10.244, p =*0.002*) . However when all the predictors are included in the equation the F change for the model is not statistically significant (F (115, 5)= .644, *p*= 0.667). In addition, the Durbin-Watson statistic is 1.921 which indicates the assumption of independent of errors has not been violated. See table 5 below.

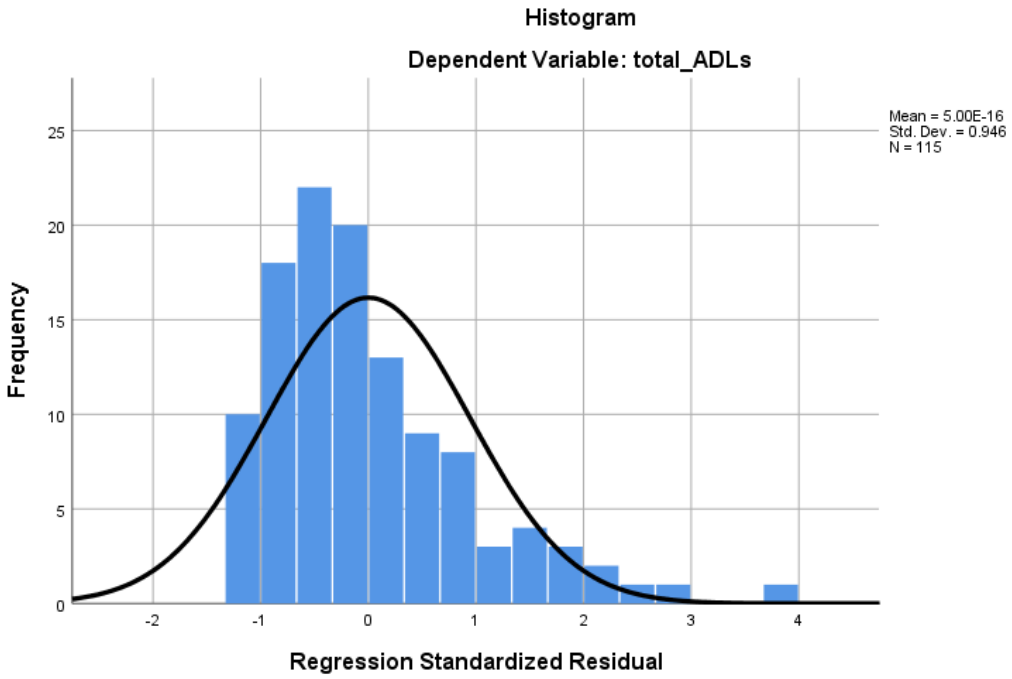
Table 5: Hierarchical Regression model: ADLs predicted by apathy, depression and potential confounding variables.

				Change statistics			
Model	R	R square	Adjusted R square	R square change	F change	Sig F change	Durbin Watson
1	.288	.083	.075	.083	10.244	.002	
2	.297	.088	.072	.005	.646	.423	
3	.417	.174	.120	.086	2.225	.057	
4	.447	.200	.105	.025	.644	.667	1.941

Table 6: Hierarchical regression: Anova table.

	Anova		
Model	df	F	sig
1	1	10.244	.002
2	2	5.429	.006
3	7	3.225	.004
4	12	2.118	.022

The independent contribution of apathy in predicting ADLs was (β = .256, p = .013) indicating that global apathy significantly predicted ADLs. On the contrary, depression did not significantly predict ADL performance (β = .164, p = .119). All the potential confounding variables that we included in the regression equation did not significantly predict ADLs except age (β = .247, p = .018). Our matrix also shows that variance infaltion factor (VIF) values are all below 10 indicating that the assumption of no multicollinearity has not been violated. The histogram below also shows that our data was normally distributed.



Principal Component Factor Analysis.

In order to establish if apathy items from the apathy evaluation scale resolved into a three factor solution as proposed by Marin (1991) we performed a principal component factor analysis. All the variables included in this analysis were all measured using the same scale and we recoded the negatively worded items from the AES so that all AES item scores can be

comparable. The mean scores of these variables are relatively similar indicating that they are a relatively similar influence of apathy. The determinant of the correlation matrix was 9.731 E-5 which is bigger than 0.00001 indicating that multi collinearity is not a problem. We also computed the Kaiser Meyer Olkin statistic (KMO) which measures sampling adequacy. This measure was above 0.5 indicating that our sample size was adequate for a factor analysis to be performed (KMO= 0.89, $p<0.001$) .

Table 7: Descriptive statistics

AES items	Mean(N=115)	Std. deviation
1.She is interested in things	2.21	1.04
2. She gets things done during the day	2.39	.984
3. Getting things started on his own is important to her	2.28	1.20
4. She is interested in having new experiences	2.77	1.12
5. She is interested in learning new things	2.95	1.08
6. She puts little effort into anything	2.46	1.12
7. She approaches life with intensity	2.63	1.10
8. Seeing a job through to the end is important to her	2.23	1.21
9. She spends time doing things that interest her	2.48	1.11
10. Someone has to tell her what to do each day	2.38	1.25
1**1**. She is less concerned about his problems than she should be	2.35	1.18
12. She has friends	2.38	1.10

13. Getting together with friends is important to her	2.70	1.19
14. When something good happens, she gets excited	1.83	.976
15. She has an accurate understanding of his problems	2.37	1.12
16. Getting things done during the day is important to her	2.30	1.12
17. She has initiative	2.68	1.19
18. She has motivation	2.61	1.13

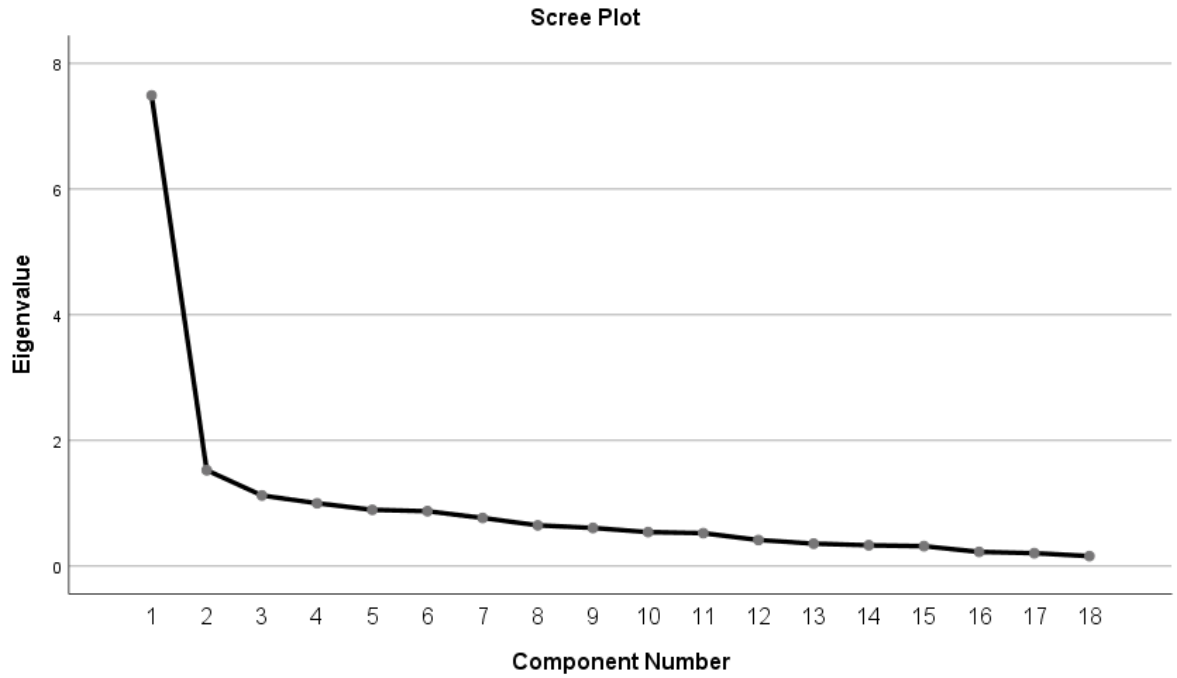
In this analysis we used the Keiser's criterion for retaining factors with associated eigenvalues of greater than 1. After extraction only 3 factors were retained with factor 1 having the highest variance (41.61%), while factor 2 and 3 had 8.4 and 6.24% of variance respectively. We also used the scree plot as our final guide on which factors to retain. The scree plot shows that the point infection is at the fourth data point. Therefore we retained the factors on the left of the data point excluding the point of inflection. Using the scree plot we then retained 3 factors. This was at par with the results of the Kaiser's criterion. In reproduced correlations, we have observed that there are 67 (43.0%) non redundant residuals with absolute values greater than 0.05. See table 8 and the scree plot below.

Table 8: Eigenvalues

	Initial Eigenvalues			Extraction Sums of squared loadings			Rotation Sums of squared loadings		
Component	Total	% of variance	Cumulative %	Total	% of variance	Cumulative %	Total	% of variance	Cumulative %
1	7.490	41.61	41.61	7.49	41.61	41.61	4.14	23.013	23.01
2	1.525	8.47	50.08	1.52	8.47	50.08	3.70	20.57	43.58
3	1.124	6.24	56.327	1.124	6.24	56.32	2.29	12.73	56.32
4	.999	5.55	61.87						
5	.894	4.96	66.84						

6	.873	4.85	71.69
7	.766	4.25	75.95
8	.648	3.60	79.55
9	.607	3.37	82.92
10	.540	3.00	85.93
11	.524	2.91	88.84
12	.415	2.30	91.14
13	.357	1.98	93.12
14	.331	1.83	94.96
15	.317	1.76	96.72
16	.225	1.25	97.98
17	.205	1.13	99.11
18	.159	.88	100.00

Figure 1



Although our analysis showed that apathy items resolved into a three factor solution, we had cross loadings of some items in 2 or three factors. See table 9. To correct this, we re ran the factor analysis but with the "problematic items" deleted as suggested by Hooper (2012). We also excluded items that Marin suggested falls under the "other" subdomain of apathy. See table 10 below. After this analysis we had factor loading after rotation showing

that items that load on the same item suggest that factor one represents cognitive apathy, factor two represents behavioural apathy and factor three represents affective apathy.

Table 9: Component matrices

	No Rotation			Orthogonal Rotation		
AES items	1	2	3	1	2	3
1.	.497			.525		
2.	.605				.629	
3	.696			.457	.506	
4.	.585	-.463		.791		
5.	.731			.819		
6.	.644			.650		
7.	.686			.560		
8	.756				.600	
9.	.653			.471		
10.	.575	.496			.758	
11		.601			.704	
12.	.537		.601			.864
13.	.530		.507			.784
14.	.507					.487
15.	.514				.419	
16.	.810			.528	.597	
17.	.861			.534	.626	
18.	.823			.625	.567	

Note: Only factors loadings above 0.4 are displayed.

Table 10

	Orthogonal Rotation		
AES items	1	2	3
1	.545		
2		.610	
4	.810		
5	.828		
6	.675		
7	.586		
9	.479		
10		.760	
11		.792	
12			.868
13			.789
14			.463

Simultaneous regression analysis

Finally, we performed a simultaneous regressed analysis to test whether the apathy subdomains we derived from our factor analysis differently predict ADL performance. We fractionated AES items largely because 1. There are indications these different forms of apathy have different neural substrates 2. They exert different challenges on ADLs. The analysis indicates that our regression model explains 96% of the variation in ADL performance. The F change was also statistically significant (F (115, 3) = 3.934, $p<0.05$) . In addition, the Durbin-Watson statistic was 2.111suggesting that the assumption of independent of errors has been met. Although our model significantly predicted ADL performance, not all of the predictors that were entered in the equations had a significant predictive effect. Behavioural apathy was the only subdomain of apathy that significantly predicted ADL performance. ($\beta = .240$, $p = .017$). Cognitive apathy ($\beta = .137$, $p = .225$) and emotional

apathy ((β = .021, p = .845) did not significantly predict ADL performance. The VIF values are all below 10 indicating that the assumption of no multicollinearity has not been violated.

Discussion

In this study we primarily had four aims. Firstly, we aimed to investigate whether depressive and apathy symptoms uniquely predict ability to perform activities of daily living in patients with AD after controlling for potential confounding variables. Although there are many variables that are known to have an impact on ADL performance in dementias, we only controlled for age, marital status, gender, level of education because they have been consistently associated with ADL performance in AD particularly (de Jager et al., 2017; ADI, 2020). Second, we aimed to establish if apathy and depression can both predict ADLs performance in our sample when entered simultaneously in a regression equation. Third, because of some evidence that apathy symptoms can be fractionated into behavioural, affective, and cognitive apathy sub-syndromes (Marin, 1991; Njomboro & Deb, 2012; Robert et al., 2009; Starkstein, 2000; van Reekum et al., 2005), we wanted to test if AES apathy items scores for our study sample resolve into this three factor solution as proposed by Marin (1991). Lastly, we wanted to establish if the apathy subdomains derived from the factor analysis predict ADLs performance differently. To our knowledge this study is the first of its kind to be conducted in this population in order to answer these particular questions. In this section, I provide a discussion for the results of my hypotheses and make reference to previous scholarly publications.

For our first aim we hypothesised that the global scores for apathy and depression will independently predict ADLs performance in our clinical sample. Our analysis confirmed this hypothesis. We found that there was a significant unique contribution of apathy in predicting

ADL performance. Similarly depression also significantly predicted the capacity to carryout ADls. These results are consistent with prior research which showed that these two neuropsychiatric syndromes predict ADLs performance (e.g., Benoit et al., 2012; Burke et al., 2019; Burns & Illife, 2009; Hernandez et al., 2012; Fujita et al., 2018; Di Iulio et al., 2010). Specifically, research on the relationship between global apathy and capacity to perform ADLs have shown that the presence of apathy symptoms in Alzheimer's disease patients is associated with a significant attenuation in their ability to carry out these ADLs. These include deficits in executing basic daily routines such as maintaining hygiene, poor diet and complex ones such as budgeting, medical adherence and shopping (Hernandez et al., 2012; Ishii et al., 2009; Wouts et al., 2019; Raimo et al., 2019). Although in our study we did not compare our cohort's ability to perform ADLs based on disease severity, there is evidence from the literature indicating that in the early manifestation of AD, patients with a comorbidity of apathy tend to have intact capacity to perform rudimentary tasks such maintain proper diet, using toilet but struggle with carrying out complex ones requiring frontal involvement such as budgeting and medical adherence (Futjita et al., 2017; Lechowski et al., 2009). This is not surprising because the ability to plan, initiate and have the motivation to carry out a goal directed behaviour is believed to require executive input which is compromised in these patients largely because neural substrates underlying this cognitive domain are dysfunctional (Chase 2011; Ginsberg, 2020; Levy & Dubois, 2006; Zhou et al., 2020). Although, our findings are consistent with past research, they do not fully explain whether global apathy relates more to instrumental activities of daily living which are known to deteriorate in the same proportion with the progression of the disease (Futjita et al., 2017; Lechowski et al., 2009) or basic ones. It is therefore possible that the association that we found in our study might be more related to IADLs and not necessarily global ADL performance. Follow up studies should therefore treat these ADLs in isolation.

Similarly, there is evidence from the literature specifically showing that depression is associated with limited capacity to carryout ADLs (Burke et al., 2019; Fujita et al., 2018). Our results are therefore supporting this trend. It also makes sense because depression in AD is known to accelerate the progression of AD, decreasing the patient's quality of life which is often evidenced by poor ADL performance (Di Iulio et al., 2010; Fujita et al., 2018; Ginsberg et al., 2019) and can also be an emotional reaction to a chronic disease such as AD.

Given that studies have demonstrated that apathy and depression are both associated with a substantial decrease in the capacity to carry out ADLs, we hypothesised that they will also significantly predict ADL performance when entered simultaneously in our regression equation. This is because these clinical syndromes are often comorbid in a number of degenerative pathologies such as AD (Benoit et al., 2012; Landes et al., 2001; Zhou; 2020). However this hypothesis was not confirmed. In this analysis, only apathy predicted ADLs performance. This is possibly due to the fact that there is a substantial overlap between apathy symptoms and depressive symptoms. For instance symptoms like anhedonia, loss of interest and reduced level of activity tend to occur in both apathetic and depressive states (Levy et al., 2005; Starkstein et al., 2005; Zhu et al., 2019). In addition most instruments that characterise depression have apathy items in them. For example, the Connell Scale for depression (Alexopoulos, 1988) used in this study has items that evaluate for loss of interest and reduced activity which can characterise both depression and apathy.

We also hypothesised that AES items will resolve into a three factor structure to indicate behavioural, cognitive and affective apathy in a manner consistent with Marin's conceptualisation of the apathy syndrome. In order to test this hypothesis, we performed a principal component factor analysis. Our analysis indicated that AES scale items indeed exhibits a three factor solution that can be categorised as affective, behavioural and cognitive apathy in analogy with Marin's conceptualisation. However, these items did not load into

these factors in the manner that was proposed by Marin (1991). Below we discuss these results.

Affective apathy

Marin (1991) suggested that two of the 18 AES items will load into affective apathy. These items are item 7 (S/he approaches life with intensity) and item 14 (When something good happens, he/she gets excited.) However, in our principal component analysis only item 14 loaded into this subdomain of apathy. It is not surprising for factor 14 to load into affective apathy because it this item describes the connection between an experience and its related/associated emotion (s). On the contrary, item 7 did not load into this subdomain but instead loaded into the cognitive cluster. One possible explanation could be that item 7 is an ambiguous statement with multiple potential interpretations. For instance, this statement could be construed to mean approaching life with enthusiasm. When understood like this, this statement relates more to emotional apathy. "S/he approaches life with intensity" can also be associated with cognitive apathy because it can mean approaching life with energy and motivation. Motivation is largely a cognitive process, which may explain how item 7 can be understood within the context or concept of cognitive apathy. In addition, the principal component matrix also showed that item 12 (S/he has friends) and item 13 (Getting together with friends is important to her/him) also load into the affective subdomain of apathy. Getting together with friends can be important to an individual because it is emotionally fulfilling. In that regard, this statement has an underlying emotional component in that it shows the emotional importance attached to having friends. It may therefore explain why this statement can be conceptually related to the affective factor. Similarly, one can have friends for the same reason. When conceptualised in this way, this statement therefore relates more to affective than other domains of apathy.

Behavioural apathy

Although the proponent of the apathy evaluation scale (Marin, 1991) indicated that 5 items in the AES load into the behavioural subdomain of apathy, our analysis showed that only 2 of those items loaded into that factor. These items were item 2 (s/he gets things done during the day) and item 10 (someone has to tell him/her what to do each day). Contrary to Marin's conceptualisation (Marin, 1991) item 6 (s/he puts little effort into anything), item 9 (s/he spends time doing things that interest him her) and item 12 (s/he has friends) did not load into this factor. Item 9 and 6 instead loaded into the cognitive subdomain. For item 9 this is possibly because the characteristic manifestation of cognitive apathy is attenuation of interest (Chase, 2011; Van Reekun, 2005). Item 6 can also be understood in the context of cognition in that putting effort into anything first needs motivational drive. It starts with a cognitive input which is then translated into a behaviour.

Cognitive Apathy

Our principal component analysis showed that of the 8 items that Marin (1991) proposed fall under cognitive apathy, only 3 of them loaded into this cluster. These are item 1 (s/he is interested in things), item 4 (s/he is interested in having new experiences) and item 5 (s/he interested in learning new things). These items collectively tap into 'interest' which is one of the indices that characterise cognitive apathy (see, Chase, 2011). Additional items identified by our component matrix that load into this factor are item 6, 7 and 9 which have been discussed in detail above. Although Marin (1991) suggested that item 3 (getting things started on his/her own is important to him/her), item 8 (seeing a job through to the end is important to her/him) and item 16 (getting things done during the day is important to her/him), as cognitive apathy indices, they did load into any of the subdomains of apathy. These three items are conceptually similar. They seem to be asking the respondents two things. For instance, "seeing a job through to the end" "and important to her/him" can be

understood to be two questions. The first part pertaining to behavioural apathy and the last part relating more to cognitive apathy. It is possible that such line of questioning could pose problems to the respondents.

In summary our analysis indicate that although Marin's conceptualisation of apathy is dominant in research (and also in some instances in clinical practice), the discrepancies between Marin's categorisation of AES symptoms and results from our analysis suggest that there can be other alternative conceptualisations. These results support suggestions advanced by other researchers who argue that apathy cannot be defined as a disorder of motivation per se (see Levy & Dubois, 2006; van Reekum, 2005). It is also possible that our conceptualisation of apathy differed somewhat from Marin's conceptualisation on the basis of psychometric reasons. For instance, to our knowledge Marin's conceptualisation was mostly based on clinical evidence rather than on robust statistical conclusions.

There is ample evidence from the literature indicating that apathy and ADLs performance are related in AD patients (e.g., Burns & Iliffe, 2009; Hernanderz et al., 2012; Ishii et al., 2009; Starkstein et al., 2006) Similarly it is widely appreciated that different subdomains of apathy differently predict ADL performance in AD patients (Njomboro & Deb 2014; Mioshi et al., 2003; Mioshi et al, 2007). However, no previous study has used apathy subdomains derived from a factor analysis to establish if they differently predict ADL performance.

In this study, we used the apathy items we derived from our factor analysis to establish if they will predict ADL performance differently. To answer this question, we regressed all apathy subdomains derived from our factor analysis on ADLs simultaneously. Our results indicated that only behavioural apathy significantly predicted ADL performance. It was expected for behavioural apathy to be significantly associated with ADL performance because past research has shown that association. For instance, (Levy & Dubois, 2006) suggested that behavioural apathy involves difficulties with activating thoughts and initiating

motor programs that are required to complete an action. Similarly, given that there is evidence showing that behavioural apathy and ADL (especially IADLs) performance attenuation was associated with fronto-parietal disturbances (Mioshi et al., 2013), we also expected this subdomain to be related with global ADL performance. We however did not expect cognitive apathy and affective apathy not to significantly predict ADL performance. This result is in contrast to what other scholars have found. For example the literature has shown that the manifestation of cognitive apathy is often associated with executive impairments which include ADLs, especially IADL (Mioshi et al., 2007; Njomboro and Debb, 2012). We note that our results might be inconsistent with previous research because of methodological differences. Studies that found the association between subdomains of apathy from the apathy evaluation scale in the original conceptualisation of Marin but our study derived them using a statistical procedure suitable for item selection/reduction.

Conclusion

In conclusion, our study suggest that the presence of apathy in AD patients has an implication in their ability to carry out their activities of daily living. Though depression also uniquely contribute to the attenuation of function in these patients, it effects seem to be diluted by the presence of apathy symptoms. This could be because apathy and depression has traditionally been treated as the same construct and most instruments assessing apathy treat it as a depressive symptom. This also has the potential to make apathy to be misdiagnosed and patients with this condition potentially enrolled in depressive medication which can worsen their symptoms. We have also shown that apathy is not only common in AD patients, but also disables the patients' capacity to carry out their daily routines more than depression which has received disproportionate clinical and scholarly attention. Therefore

clinical and empirical focus on this syndrome in dementias should thus be accelerated. Apathy is also largely understood through the lens of Marin's conceptual framework. However, our study demonstrated that though apathy (AES items) can be categorised into cognitive, behavioural and affective subdomains in line with Marin's proposal, they do not cluster in the same manner he proposed. This suggest that it might be useful to treat apathy as a multi-dimensional condition in both research and interventions. This approach might also be useful because as our study showed, different subdomains of apathy predict ADL performance differently. Behavioural apathy was the only subdomain that associated with ADL performance in our sample. This might mean that the behaviour that is necessary to execute ADLs is compromised in this patients and as such treatment should be directed at behavioural outcomes of apathy in AD patients.

Limitations and recommendations

We note that our study had some limitations. The sample size of this study was small and might have affected our results. These results should therefore be interpreted cautiously. In addition, we used a homogenous sample which might also affected the validity of our results. Future research should envisage to replicate this study using large heterogeneous sample. We were also unable to explain if the relationship we found between apathy and ADLs was related to different categories of ADLs or globally. Follow up research should address that gap. Our study did not control for disease severity which is known to be associated with defective ADL performance. It is possible that the association we found between our neuropsychiatric outcomes and ADLs might have been compounded by the severity of Alzheimer's disease in our sample. Subsequent studies should aim to control for such potential effects. Lastly, given that there is substantial overlap between affective symptoms of depression and apathy which might have influenced our results, future research should try to isolate these affective symptoms.

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APPENDIX

Appendix A

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: preaward@curie.uct.ac.za

04 April 2007

REC REF: 152/2007

Dr S Kalula
Geriatric Medicine

Dear Dr Kalula

PROJECT TITLE: APPLICATION FOR BLANKET ETHICAL APPROVAL FOR MEMORY CLINIC DATA.

Thank you for your letter to the Research Ethics Committee dated 23rd March 2007.

I have pleasure in informing you that the Ethics Committee has **formally approved** the above mentioned study.
Please inform the Committee of each study being performed.

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROF M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

pp

lemjedi

Appendix B

MEMORY CLINIC

Clerking Notes

Scales

Folder number:								**Record number:**			

Patient: _____

				2	0		

***Examiner*:**

- *Ensure patient identification information is recorded above.*

- *Enter scores at corresponding numbers in the<u>Assessment Information Booklet</u>*

Section N: Scales

Administer the scales as appropriate. Enter the score in each case in Section N in the Assessment Information Booklet.

N1 Bristol Activities of Daily Living Scale (modified)

N2 Cornell Scale for Depression

N3 Apathy Evaluation Scale (Informant)

N1 **Bristol Activities of Daily Living Scale (modified)**

Instruction: *C*ircle the response that best describes the patient's level of ability to perform that activity. Only one box should be marked for each activity. Where in doubt, choose the level of ability which represents the patient's average performance over the past two weeks.

1. **Food**

A Selects and prepares food	0
B Able to prepare food only if ingredients are set out	1
C Able to prepare food only if shown step by step	2
D Unable to prepare food	3
E Not applicable	0

2. **Eating**

A Eats as previously	0
B Eats appropriately if food is made manageable and/or uses a spoon	1
C Needs someone to help guide food to mouth	2
D Needs to be fed	3
E Not applicable	0

3. **Drink**

A Able to make tea/coffee as previously	0
B Able to make tea/coffee only if ingredients are set out	1
C Able to make tea/coffee only if shown step by step	2
D Unable to make tea/coffee	3
E Not applicable	0

4. **Dressing**

A Dresses as previously	0
B Puts clothes on incorrectly or inappropriately	1
C Unable to dress self but moves limbs to assist	2
D Has to be dressed	3
E Not applicable	0

5. **Hygiene**

A Washes self as previously	0
B Able to wash self if given soap, towel and water	1
C Able to wash self but needs help	2
D Has to be washed	3
E Not applicable	0

6. **Teeth**

A Cleans teeth as previously	0
B Cleans teeth only if given water and toothpaste or gargle	1
C Able to clean teeth but needs help	2
D Unable to clean teeth	3

E	Not applicable	0

7. **Toilet**

A Uses toilet as previously	0
B Able to use toilet (or bucket) if helped	1
C Incontinent of urine	2
D Incontinent of urine and faeces	3
E Not applicable	0

8. **Transfers**

A Able to get in/out of a chair as previously	0
B Able to get in a chair but needs help to get out	1
C Needs help getting in/out of a chair	2
D Has to be lifted in/out a chair	3
E Not applicable	0

9. **Mobility**

A Walks independently	0
B Walks with assistance, i.e. furniture, arm for support	1
C Uses aid to walk, i.e. cane, frame	2
D Unable to walk	3
E Not applicable	0

10. **Orientation –Time**

A Fully orientated to time/day/date, etc.	0
B Unaware of time/day/date but seems unconcerned	1
C Repeatedly asks the time/day/date	2

D Mixes up night and day	3
E Not applicable	0

11. **Orientation – Space**

A Fully orientated to surroundings	0
B Orientated to familiar surroundings only	1
C Gets lost in home, needs reminding where toilet is	2
D Does not recognise own home	3
E Not applicable	0

12. **Communication**

A Able to hold appropriate conversation	0
B Understands others and tries to respond verbally with gestures	1
C Can make self understood but has difficultyunderstanding others	2
D Does not respond to or communicate with others	3
E Not applicable	0

13. **Telephone**

A Uses telephone appropriately	0
B Uses telephone with help	1
C Answers telephone but does not make calls	2
D Unable/unwilling to use telephone	3
E Not applicable	0

14. **Housework/gardening**

A	Able to do housework/gardening to previous standard	0
B	Able to do housework/gardening but not to previous standard	1
C	Limited participation in housework/gardening	2
D	Unwilling/unable to participate in previous housework/gardening activities	3
E	Not applicable	0

15. **Shopping**

A	Shops to previous standard	0
B	Only able to shop for 1 or 2 items without a list	1
C	Unable to shop alone, but participates when accompanied	2
D	Unable to participate in shopping even when accompanied	3
E	Not applicable	0

16. **Finances**

A	Manages own finances as previously	0
B	Recognises money values and can sign name	1
C	Does not recognise money values but can sign name	2
D	Unable to sign name or recognise money values	3
E	Not applicable	0

17. **Transport**

A	Able to drive, cycle or use public transport independently	0
B	Unable to drive but uses public transport, bike, etc.	1

C	Unable to use public transport alone	2
D	Unable or unwilling to use public transport even when accompanied	3
E	Not applicable	0

Score: Add encircled numbers for 17 activity domains

Maximum Score: 51 ☐

Total "not applicable" activities ☐

2. **Cornell Scale for Depression**

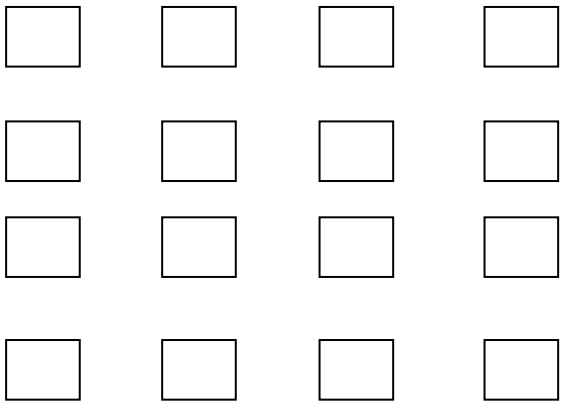
Instruction: Tick the appropriate box for each item.

	Unable to evaluate (U)	Absent (0)	Mild or intermittent (1)	Severe (2)
A. **Mood-related signs**	☐	☐	☐	☐
1 Anxiety (anxious expression, ruminations, worrying)	☐	☐	☐	☐
	☐	☐	☐	☐
2 Sadness (sad expression, sad voice, tearfulness)	☐	☐	☐	☐

3 Lack of reactivity to pleasant events

4 Irritability
(easily annoyed, short-tempered)

B. **Behavioural disturbances**



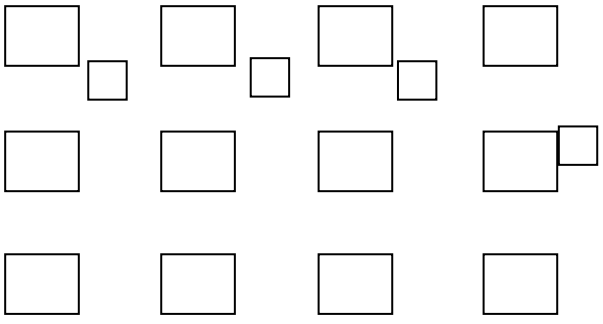
5 Agitation
(restlessness, hand-wringing, hair pulling)

6 Retardation
(slow movements / speech / reaction)

7 Multiple physical complaints (*score 0 if GI symptoms only*)

8 Loss of interest
(less involved in usual activities; *score only if change occurred acutely, i.e. in less than one month*)

C. **Physical signs**



9 Appetite loss
(eating less than usual)

10 Weight loss
(*score 2 if greater than 2 kilos in one month*)

11 Lack of energy
(fatigues easily, unable to sustain activities; *score only if change occurred acutely, i.e. in less than one month*)

	Unable to evaluate (U)	Absent (0)	Mild or intermittent (1)	Severe (2)
D. **Cyclic functions**				
12 Diurnal variation of mood (symptoms worse in the morning)		☐		
13 Difficulty falling asleep (later than usual for this individual)		☐	☐	☐
14 Multiple awakenings during sleep		☐	☐	☐
15 Early morning awakening (earlier than usual for this individual)		☐	☐	☐
E. **Ideational disturbance**				
16 Suicide		☐	☐	☐

(feels life is not worth living, has suicidal wishes, or
makes suicide attempts)

17 Poor self-esteem
(self-blame, self deprecation, feelings of failure)

18 Pessimism
(anticipation of the worst)

19 Mood-congruent delusions
(delusions of poverty, illness or loss)

Score: Add the number received for each item.

Score < 6: Absence of depressive symptoms

Score >10: Probable major depression

Score >18: Definite major depression

Maximum Score: 38 ☐

Total unable to evaluate ☐

Apathy Evaluation Scale (Informant)

Name: _____ Date: ___/___/___

Informant's Name: _____ Relationship:_____

For each statement, circle the answer that best describes the subject's thoughts, feelings, and activity in the past 4 weeks.

1. S/he is interested in things.

NOT AT ALL (4) SLIGHTLY (3) SOMEWHAT (2) A LOT (1)

2. S/he gets things done during the day.

NOT AT ALL (4) SLIGHTLY (3) SOMEWHAT (2) A LOT (1)

3. Getting things started on his/her own is important to him/her.

NOT AT ALL (4) SLIGHTLY (3) SOMEWHAT (2) A LOT (1)

4. S/he is interested in having new experiences.

NOT AT ALL (4) SLIGHTLY (3) SOMEWHAT (2) A LOT (1)

5. S/he is interested in learning new things.

NOT AT ALL (4) SLIGHTLY (3) SOMEWHAT (2) A LOT (1)

6. S/he puts little effort into anything.

NOT AL ALL (1) SLIGHTLY (2) SOMEWHAT (3) A LOT (4)

7. S/he approaches life with intensity.

NOT AT ALL (4) SLIGHTLY (3) SOMEWHAT (2) A LOT (1)

8. Seeing a job through to the end is important to him/her.

NOT AT ALL (4) SLIGHTLY (3) SOMEWHAT (2) A LOT (1)

9. S/he spends time doing things that interest him/her.

NOT AT ALL (4) SLIGHTLY (3) SOMEWHAT (2) A LOT (1)

10. Someone has to tell him/her what to do each day.

NOT AT ALL (1) SLIGHTLY (2) SOMEWHAT (3) A LOT (4)

11. S/he is less concerned about her/his problems than s/he should be.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
(1)	(2)	(3)	(4)

12. S/he has friends.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
(4)	(3)	(2)	(1)

13. Getting together with friends is important to him/her.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
(4)	(3)	(2)	(1)

14. When something good happens, s/he gets excited.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
(4)	(3)	(2)	(1)

15. S/he has an accurate understanding of her/his problems.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
(4)	(3)	(2)	(1)

16. Getting things done during the day is important to her/him.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
(4)	(3)	(2)	(1)

17. S/he has initiative.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
(4)	(3)	(2)	(1)

18. S/he has motivation.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
(4)	(3)	(2)	(1)

The Apathy Evaluation Scale was developed by Robert S. Marin, M.D. Development and validation studies are described in RS Marin, RC Biedrzycki, S Firinciogullari: "Reliability and Validity of the Apathy Evaluation Scale, "*Psychiatry Research*, 38:143-162, 1991.

Total score ☐